

## REMARKS

Claims 1-4 and 42-50 appear in this application for the Examiner's review and consideration. Applicants have cancelled claim 51 without prejudice.

Claims 1-3 and 42-51 stand rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the written description requirement for the reasons set forth on pages 2-4 of the Office Action. Applicants respectfully traverse.

The rejection is moot in view of the amendment to the claims. Thus, the rejection of claims 1-3 and 42-51 under 35 U.S.C. § 112, first paragraph, cannot stand and should be withdrawn.

Claims 1-3 and 42-51 stand rejected under 35 U.S.C. § 103(a) as allegedly rendered obvious over Zhongguo Yiyao Gongye Zazhi 24, 241-242 (1993) ("the Zhongguo reference"), U.S. patent Nos. 4,845,115 to Tyers *et al.*, ("the '115 patent"), 4,695,578 to Coates *et al.*, ("the '578 patent"), 4,835,173 to Tyers ("the '173 patent"), and PCT publication WO 02/36558 ("the WO '558 publication") for the reasons set forth on pages 8-14 of the Office Action. Applicants respectfully traverse.

The consistent criterion for determination of obviousness is whether the prior art would have suggested to one of ordinary skill in the art that claimed subject matter should be carried out and would have a reasonable likelihood of success. *In re Dow Chemical Co.*, 837 F.2d 469, 473, 5 U.S.P.Q.2d 1529, 1531 (Fed. Cir. 1988). As the Examiner is well aware, in order to form a proper basis for a rejection under 35 U.S.C. § 103, the prior art must provide some suggestion, either explicit or implicit, of the combination that allegedly renders a claimed invention obvious. *M.P.E.P.*, § 2142 (June 1998), *see also, Panduit Corp. v. Denison Manufacturing Co.*, 1 U.S.P.Q.2d 1593, 1597 (Fed. Cir. 1987). The Examiner can satisfy the burden of showing obviousness of the combination only by showing some objective teaching in the prior art or that knowledge generally available to one of ordinary skill in the art would lead that individual to combine the relevant teachings of the references. *In re Sang Su Lee*, 277 F.3d 1338, 1343, 61 U.S.P.Q.2d 1430 (Fed. Cir. 2002); citing *In re Fritch*, 972 F.2d 1260, 1265, 23 U.S.P.Q.2d 1780, 1783 (Fed. Cir. 1992). The need for specificity is paramount, particular findings must be made as to the reason the skilled artisan, with no knowledge of the claimed invention, would have selected the components for combination in the manner claimed. *Id.* The Examiner's conclusory statements do not adequately address the issue of motivation to combine; the factual question of motivation is material to patentability, and can not be resolved on subjective belief and unknown authority. *Id.*

In the case of compounds, “[u]ntil the claimed compounds were actually isolated and purified, it would have been unlikely for one of ordinary skill in the art to contemplate what was ultimately obtained; what cannot be contemplated or conceived cannot be obvious.” *In re Deuel*, 51 F.3d 1552, 1558, 34 U.S.P.Q.2d 1210 (Fed. Cir. 1995). In particular case, the courts repeatedly have held that a pure compound may be patentable over the impure compound. As early as 1964, the United States Court of Customs and Patent Appeals repeated this proposition:

No doctrine of the patent law is better established than that a prior patent or other publication to be an anticipation must bear within its four corners adequate directions for the practice of the patent invalidated. **If the earlier disclosure offers no more than a starting point for further experiments**, if its teaching does not inform the art without more how to practice the new invention, it has not correspondingly enriched the store of knowledge, and **it is not an anticipation**.

*In re Seaborg*, 382 F.2d 996, 997 (C.C.P.A. 1964) (emphasis added). No more than six years later again the C.C.P.A. held that pure materials are patentable.

... whether the claimed pure materials are novel as compared with the less pure materials of the reference. It seems to us that the answer to question is self-evident: by definition pure materials necessarily differ from less pure or impure materials and, if the latter are the only ones existing and available as a standard of reference, as seems to be the situation here, perforce the “pure” materials are “new” with respect to them.

*In re Bergstrom*, 427 F.2d 1394, 1402 (C.C.P.A. 1970) (emphasis added).

Furthermore, the courts consistently have refuse to apply a broad proposition of unpatentability. “The cited cases fail to support the broad proposition that merely changing the form, purity or another characteristic of an old product, the utility remaining the same as that of the old product, does not render the claimed product patentable.” *In re Cofer*, 354 F.2d 664, 667 (C.C.P.A. 1966).

The claims recite “Ondansetron hydrochloride dihydrate having a purity of at least about 99.0% and an exo-methylene content of less than 0.01%.”

Throughout prosecution, applicants have repeatedly set forth that the cited art does not disclose or suggest either explicitly or inherently the purity of the compound recited in the claims. The Zhongguo reference discloses ondansetron dihydrate with no mention of purity. The Example 2 of the ‘115 patent discloses a method of making ondansetron

hydrochloride dihydrate and reports a water content of 10.23% by assay. Despite recrystallizing ondansetron HCl dihydrate in water and isopropanol, the '115 patent does not disclose purity or the presence of exo-methylene. Example 10 of the '578 patent discloses verbatim the method of making ondansetron hydrochloride dihydrate as Example 2 of the '115 patent. Both examples are identical including the recrystallization procedure, the water content (10.23%) by assay, and the failure to disclose the ondansetron HCl dihydrate purity. The WO '558 publication discloses methods of making ondansetron HCl dihydrate, but fails to disclose any purity. Applicants have submitted a declaration under 37 C.F.R. 1.132 demonstrating that the prior art was unable to obtain the recited purity.

The Office Action again maintains that “[t]he difference between the instant claimed invention and the prior art is that the prior art is silent as to purity of the product obtained.” For motivation, citing *Ex parte Hartop*, the Office Action proposes “[c]hanging the form, purity, color, or other characteristic of an old product without a new use as a result thereof does not render [sic] product patentable where utility remains the same.” *Ex parte Hartop*, 139 U.S.P.Q. 525 (B.P.A.I. 1962). In a conclusory statement the Office Action proposes that “[o]ne of ordinary skill in the art would be motivated to prepare a purer form of a known organic pharmaceutically active compound [sic, with] in the expectation of obtaining that very compound but with enhanced properties, e.g. improved solubility, shelf-life, improved mode of administering properties, etc.” See Office Action p. 10.

The new use requirement of *Ex parte Hartop* is no longer necessary. This decision by the Board of Patent Appeals and Interferences is no longer applicable. The Federal Circuit *In re Cofer* clearly sets forth that new utility is not required. Therefore, only the second argument proposed by the Office Action can provide the necessary motivation. However, this second argument is merely an “obvious to try” argument, an invitation to experiment at best. Without pointing out where the cited references would suggest such motivation, the Office Action concludes that purer forms of a known organic pharmaceutically active compound are desirable. Without further demonstrating how to achieve such forms or whether there is any methodology that would be successful, the Office Action concludes that it’s just obvious to do it. The law, however, requires more.

The need for specificity is paramount, particular findings must be made as to the reason the skilled artisan, with no knowledge of the claimed invention, would have selected the components for combination in the manner claimed. The Examiner’s conclusory statements do not adequately address the issue of motivation to combine; the factual question

of motivation is material to patentability, and can not be resolved on subjective belief and unknown authority.

The Office Action proposes that it would be obvious for someone to try to obtain “a purer form of a known organic pharmaceutically active compound.” This proposition, however, is merely a generic invitation to try to obtain a purer compound. It is not specific to the recited ondansetron and is not supported by any of the cited references. This hindsight analysis is exactly what the Federal Circuit cautioned against in *In re O'Farrell*:

The admonition that “obvious to try” is not the standard under § 103 has been directed mainly at two kinds of error. In some cases, what would have been “obvious to try” would have been to vary all parameters or to try each of numerous possible choices until one possibly arrived at a successful result, where the prior art gave either no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful.

*In re O'Farrell*, 853 F.2d 894, 903 (Fed. Cir. 1988).

Therefore, without using hindsight analysis, there is nothing in the cited references that would suggest to the skilled artisan the recited purity levels.

Accordingly, the rejection of claims 1-4 and 42-51 under 35 U.S.C. § 103(a) as rendered obvious by the Zhongguo reference, the '115 patent, the '578 patent, the '173 patent, or the WO '558 publication cannot stand and should be withdrawn.

Accordingly, it is believed that claims 1-4 and 42-51 are now in condition for allowance, early notice of which would be appreciated.

If any outstanding issues remain, the examiner is invited to telephone the undersigned at the telephone number indicated below to discuss the same. No fee is believed to be due for the submission of this response. Should any fees be required, please charge such fees to Kenyon & Kenyon, LLP Deposit Account No. 11-0600.

Respectfully submitted,

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